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Review

Should we routinely use modified Atkins diet instead of regular ketogenic diet to treat children with epilepsy?

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ABSTRACT

The modified Atkins diet (MAD) consists of a nearly balanced diet without any age-dependent restriction of recommended daily calorie intake. Recently, there has been a marked increase in the use of the MAD in the treatment of epilepsy. Over the last 8 years, evidence suggesting that the MAD may exhibit similar anticonvulsant properties as the traditional ketogenic diet (KD) has been accumulating. KD is now an 'evidence-based' treatment for refractory epilepsy. Although there are currently no direct comparisons data from the literature suggest that the KD is more efficacious than the MAD. However, the MAD is easier to administer and has better tolerability. This review discusses when to consider each diet. The MAD may be the first diet of choice. In case of insufficient efficacy under the MAD, a switch from the MAD to the KD should be considered.

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The modified Atkins diet (MAD) consists of a nearly balanced diet (60% fat, 30% protein, and 10% carbohydrates by weight), without any restriction on the recommended daily calories according to patient age. In 2003, this less restrictive form of the ketogenic diet (KD) was first reported to potentially be an effective treatment for children and adults with epilepsy.[1] Over the last nine years, accumulating evidence has suggested that the MAD may be as efficacious as the traditional KD. Today, the MAD is no longer considered to be a new treatment.

The KD is now a proven, 'evidence-based' treatment of refractory epilepsy.[2] The classical KD is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1. Fat is provided as long-chain triglycerides. Protein intake is restricted to the minimum requirements for growth, and carbohydrate sources are mostly limited to small portions of vegetables or fruit. The efficacy of the KD has been proven by several multicentre trials and one randomised trial;[2–5] 40–50% of children on the KD experience a 50% or greater reduction in seizure frequency. Moreover, the KD seems to be a particularly effective treatment of some epileptic syndromes, such as infantile spasms, Lennox–Gastaut syndrome and myoclonic–astatic epilepsy.[4,6–8]

The MAD was originally designed and investigated at Johns Hopkins Hospital (JHH). The JHH team aimed to propose a less restrictive dietary treatment that would be more palatable to children and adolescents with behavioural difficulties whose parents and neurologists were reluctant to start on the traditional KD.[9] The diet is "modified" from the classical Atkins diet in three ways: the "induction phase" of the diet, during which carbohydrates are limited, is maintained indefinitely; fat is encouraged (not just allowed); and weight loss is not the goal (unless nutritionally indicated).

The purpose of this review is to summarise available data on the MAD efficacy (PubMed Search from January 2000 to June 2011; MeSH: "Epilepsy AND Atkins Diet") and then to discuss recent data that may suggest a new step in dietary treatments of epilepsy.

1. Available data on the MAD: an effective dietary treatment of refractory epilepsy

More than 10 studies including children or adults have investigated the effectiveness of the MAD as a dietary treatment of refractory epilepsy.[10–19] Many of these studies have been conducted prospectively. I summarised the data from these studies in Table 1 (studies conducted in children) and Table 2 (studies conducted in adults). These studies include about 160 patients with refractory epilepsy who were put on the MAD. Considering the epilepsy syndrome of the patients treated with the MAD, it is very unlikely that the high level of efficacy of the diet, as assessed by a reduction in seizure frequency, can be explained by a GLUT 1 deficiency. After three months on the diet, 48% of patients (73/152) experienced greater than a 50% reduction in seizure frequency.

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Table 1
Data from the published studies on Atkins diet in children. The responder rate (>50% seizure reduction) is reported when available. We also determine the total of responders from the available study at 1 month, 3 month and 6 months under modified Atkins diet.

		n	1 month	3 month	6 month
Kossoff et al.[13]	Propective/children	20	14/20	13/20	13/20
Kang et al.[11]	Prospective/children	14	8/14	7/14	5/14
Porta et al.[14]	Retrospective/children	10	5/10	2/10	NA
Weber et al.[15]	Prospective/children	15	NA	6/15	NA
Miranda et al.[16]	Prospective/children	33	NA	17/33	13/33
Groomes et al.[19]	Retrospective/children Absence epilepsy	13	10/13	12/13	NA
Total		105	37/57 (65%)	57/105 (54%)	31/67 (46%)

NA, not available.

Table 2
Data from the published studies on Atkins diet in adults. The responder rate (>50% seizure reduction) is reported when available. We also determine the total of responders from the available study at 1 month, 3 month and 6 months under modified Atkins diet.

		n	1 month	3 month	6 month
Kossoff et al.[9]	Prospective/adults	30	14/30	14/30	10/30
Carrette et al.[10]	Prospective/adults	8	NA	NA	1/8
Smith et al.[17]	Prospective/adults	18	NA	2/17	4/14
Total		56	14/30 (47%)	16/47 (34%)	15/52 (29%)

NA, not available.

This level of efficacy remains high at 6 months, with 39% of patients (46/119) experiencing a similar reduction in seizure frequency.[10–17,19] About 80% (119/148) of the patients remain on the MAD for 6 months (Tables 1 and 2). These studies suggest that the MAD is an effective treatment for refractory epilepsy. Most of the authors reported a high degree of acceptance among patients that can be related to the less restrictive dietary rules. Examining the available data, the efficacy of MAD might appear to be higher in children than in adults. However, the numbers of children and adults included in these studies are quite different. Conclusions on the relationship between efficacy and age cannot be drawn because of the varying methods used.

2. Side effects in MAD

It has been suggested that the risk of growth impairment, kidney stones and dyslipidaemia might be lower on the MAD than on the KD since the MAD allows for increased protein consumption and decreased fat intake. However, no study is available to confirm this hypothesis. The published literature has left the long-term side effects of the MAD relatively unexplored. Some 'side' effects might be considered beneficial. Weight loss can occur in children and adults who are overweight. Other beneficial effects have also been reported, such as "improved concentration, well-being and fitness," "more erect posture," "more fluent speech," and improved mood.[10]

The most common side effects of the MAD are gastrointestinal complaints and unfavourable lipid profiles. In the published studies, 4 of 92 patients discontinued the MAD because of side effects ($n = 1$ vomiting, $n = 1$ headaches), and 8/92 discontinued the MAD because of intolerance.[10–12,15,17,18] Kossoff et al. reported that most adults did not have to discontinue MAD because of abnormal laboratory results.[12] Moreover, Kang et al. reported only transient hyperlipidaemia.[11] In a large study, slight fatigue was observed in one-third of the patients.[16] I found four studies that detailed the incidence of MAD side effects.[10,11,15,17] Regarding gastrointestinal side effects, nausea occurred in 2/21 patients; diarrhoea, 3/21; and constipation, 6/21.[10,15] Three out of seven patients reported feeling weak. Kang et al. reported gastrointestinal disturbances in six of 14 patients (vague abdominal pain, constipation, vomiting and diarrhoea); they did not provide more details. Smith et al. stated that none of their patients discontinued the diet because of side effects or abnormal laboratory results; they also did not observe patients with constipation.[17]

3. Does MAD have the same efficacy than KD?

A recent prospective study conducted in Denmark suggested that the efficacy of the MAD is similar to that of the KD.[16] Thirty-three children with medically resistant epilepsy who were placed on the MAD were included. Three months after the start of the diet, 17/33 patients (52%) experienced a reduction in seizures of at least 50%. Out of these patients, 14 patients (42%) reported seizure reductions of greater than 90% after 3 months on the diet. In addition, 17 patients (52%) remained on the MAD for at least 12 months. Nine of seventeen patients (27% of the 33 included patients) experienced greater than 50% seizure reduction. To evaluate the efficacy of the MAD compared with the KD, the authors compared their data to a previous study conducted at the same centre.[20] The percentage of responders (patients who experienced >50% seizure reduction) after 6 months on the MAD were compared with the percentage of responders previously treated by the KD.[16] The authors did not observe any significant difference between the treatment groups. A strong trend for a higher percentage of responders was observed in the KD group (MAD 39% vs. KD 60%, $p = 0.06$). However, the patients in the KD group were significantly younger than the patients in the MAD group. When the authors adjusted the 2 groups for the difference in age, this trend disappeared.[16]

Recently, a study aimed to determine whether switching from the MAD to the KD would improve seizure control. The effect of the MAD was retrospectively studied in 27 patients.[21] During treatment with the MAD, 19 subjects (70%) experienced at least a 50% reduction in seizures, and 5 children in this study demonstrated no improvement. After switching to the KD, the responder rate remained stable (19 patients (70%)); however, 10 patients (37%) experienced a 10% greater seizure reduction while on the KD than while on the MAD, and 5 children became seizure-free. The major finding of this study was that only children who experienced a reduction in seizures while on the MAD subsequently improved after switching to the KD. The KD may slightly improve seizure control in approximately one-third of children

Table 3
Proposal on the use of modified Atkins diet (MAD) and ketogenic diet (KD)in various epilepsy syndromes based on the benefit-risk ratio.

In case of dietary treatment, the use of KD may be switched to MAD after proved efficacy
Infantile spasms – West syndrome
Myoclonic astatic epilepsy
Worsening epilepsy (any epilepsy syndrome)
Status epilepticus
In case of dietary treatment, the use of MAD may be switched to KD to improve efficacy
Absence epilepsy
GLUT-1 deficiency

previously treated with the MAD. However, no child who did not improvement while on the MAD improved while on the KD. This finding suggests that these diets are probably a unique therapy in which KD is more effective. Note that of the patients who became seizure free, all had myoclonic–astatic epilepsy.

In conclusion, the MAD may be slightly less efficacious compared with the KD. Only a randomised trial comparing the MAD and KD would definitively answer this question. However, the results of the Kossof et al. study on the switch from MAD to KD strongly support the idea that KD could be more efficient, effectively representing a ''higher dose'' of dietary treatment.[21]

4. When dietary treatment of epilepsy is considered, should we use MAD or KD first? (Table 3)

When a dietary treatment is discussed for a patient with epilepsy, I suggest that treatment should be selected like an antiepileptic drug (AED) is selected. The choice of an AED is based on the balance between benefits and risks, the spectrum of efficacy for the epileptic syndrome, the tolerability and its pharmacologic properties.

In the case of a recent diagnosis of epileptic encephalopathies, the choice should be based mostly on the efficacy of the diet to control seizure (e.g., infantile spasms). The KD should then be considered. If the dietary treatment is considered to be an emergency rescue treatment as in status epilepticus (SE), we also recommend the KD. Accumulating data suggest the efficacy of the KD in the case of refractory SE.[22–24] It would be possible to switch to the MAD after the KD has provided partial or total seizure control. The switch from one diet to the other has been reported in a few cases without increasing the seizure frequency.[14]

If the KD or MAD results in full seizure control, I recommend that the possibility of GLUT-1 deficiency be investigated. Recent data suggest that GLUT-1 deficiency may be the underlying cause of myoclonic–astatic epilepsy in 5% of patients,[25] and the KD has been observed to be a particularly effective treatment of myoclonic–astatic epilepsy.[7,21] Moreover, accumulating data suggest that GLUT-1 deficiency could be observed in a wide clinical spectrum.[26–31] A diagnosis of GLUT-1 deficiency would not exclude the use of the MAD. In these patients, the switch from KD to MAD should be carefully managed because little data are available.[32]

If a dietary treatment is considered for a patient with epilepsy that does not require rapid seizure control or a patient with epileptic encephalopathy at a chronic phase, I propose to start the MAD, which is effective but better tolerated. Patients who experience limited MAD efficacy should be switched to the KD since an additional improvement may be observed.[21] The use of a 'Ketocomplement' can also be considered to improve MAD efficacy.[33] In a study involving 30 children with intractable epilepsy, the MAD was initiated in combination with a daily 400-calorie KetoCal® shake. This diet was more effective than the usual MAD,[33] and this combination may also be considered in case of insufficient seizure control on the usual MAD.

Most of the studies investigating the use of dietary treatments of specific epilepsy syndrome have been conducted with KD; however, now, there are a few reports on the effect of the MAD in defined epilepsy syndromes. One study investigated MAD efficacy for the treatment of absence epilepsies in 21 patients (9 KD and 12 MAD); 18 patients (82%) experienced >50% seizure reduction. Of these 18 patients, 10 patients (48%) experienced a >90% seizure reduction, and 4 patients (19%) were seizure free. Nine of 12 patients treated by the MAD exhibited a seizure improvement (>50%).[19] The successful use of the MAD has also been reported in two children with non-convulsive status epilepticus.[34]

5. Lessons from studies on the MAD regarding the mechanisms of action of dietary treatment

Examining the data from the studies on the MAD, it is possible to discuss the mechanisms underlying the dietary treatment of epilepsy (KD and/or MAD). In the study conducted by Kang et al., the children who experienced a greater reduction in seizures exhibited fewer fluctuations in serum ketosis.[11] Limited data are available regarding the value of serum β-hydroxybutyrate (B-OH), but one study suggested that serum B-OH may correlate with seizure control.[35]

An interesting finding of the first paediatric study on the MAD was that a stable body mass index (BMI) (changing less than 0.3 over the 6-month study period) correlates with seizure reduction whereas weight loss did not.[13] Experimental data have suggested that caloric restriction exhibits anticonvulsant properties.[36,37] However, it is currently impossible to clearly determine the role of caloric restriction in the KD or MAD.

More recently, a clinical study conducted at JHH also suggested that the amount of lipids allowed may play a role in the anticonvulsant properties of the KD and MAD. Thirty children with intractable epilepsy were prospectively started on the MAD in combination with a daily 400-calorie KetoCal® shake.[33] At 1 month, 24 (80%) children experienced >50% seizure reduction, of which 11 children (37%) experienced >90% seizure reduction. A true control group was not used in their study; however, the authors compared their data with published reports investigating the use of the modified Atkins diet. They found a higher number of responders (>50% seizure reduction) in their patients than in the patients from these studies (37 of 64, 58%, $p = .03$). The authors have hypothesised that KetoCal® would improve ketosis. However, they did not find any clear increase of ketosis in their patients compared with patients on the usual modified Atkins diet. The daily fat intake was definitively higher in their patients suggesting a critical role of fatty acids in the mechanism of action of dietary therapies. In these patients, caloric intake was also increased, suggesting that caloric restriction, theorised by some as a mechanism of action for dietary treatments, did not appear to be important.[33] Experimental data have also shown that fatty acids, in particular polyunsaturated fatty acids, exhibit anticonvulsant properties.[38]

The hypothesis that the KD and MAD may act or share similar underlying mechanisms need to be further studied.

6. Conclusion

Currently, we have sufficient data to state that MAD is an efficacious dietary treatment of epilepsy. Existing data are not sufficient to draw conclusions about MAD efficacy relative to KD efficacy. It is currently difficult to conclude that the efficacy of the MAD is similar to that of the KD. A controlled trial is needed. However, MAD can be used as a first dietary treatment because it

has a favourable risk-benefit ratio. The MAD is more palatable and less restrictive than the KD. It is important to remember that the KD has been shown to further improve patients who responded to the MAD. The KD should be considered instead of the MAD in some epilepsy syndromes when rapid improvement is required, in particular when this may affect the outcome or in some epileptic encephalopathies where KD is particularly effective.

Conflict of interest

The author has no conflict of interest to declare.

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